PATENT
Docket no. 1254-0195P

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant: Yusuke NAKAMURA et al. Conf.: 7091

Appl. No.: 10/060,301 Art Unit: 1637

Filed: February 1, 2002 Examiner: Y. J. Kim

For: A METHOD FOR SNP (SINGLE NUCLEOTIDE POLYMORPHISM) TYPING

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

I, Dr. Yusuke Nakamura, hereby declare as follows:

1. I am a Japanese citizen, receiving mail at 1-17-33, Azamino, Aoba-ku, Yokohama-shi, Kanagawa 225-0011, Japan.

2. I am presently employed as Director of Center for Genomic Medicine in RIKEN. A copy of my Curriculum Vitae is attached.

3. I am a co-inventor of the subject matter of the above-identified U.S. Patent application. I am familiar with the specification and pending claims, and with the prosecution history of the application.

4. The Examiner has rejected claims 1, 3, 5 and 7 of the application as being obvious in view of Mein et al., *Genome Research* 10:330-343 (2000) in view of Wang et al., *Science* 280:1077-1082 (1998). Furthermore, claims 2, 6 and 8 are rejected as being obvious over Mein et al. and Wang et al. in further view of Brooks et al., U.S. 2001/0046670.

5. The Examiner asserts that Mein et al. disclose multiplex amplification of polymorphic loci followed by detection of SNPs by an INVADER assay method. In the Mein reference, 36 SNP sites were typed by 10 ng of DNA. The Examiner admits that both the number of primer pairs and the amount of DNA used by Mein et al. are outside the scope of the present claims.

6. The Examiner asserts that Wang et al. disclose detection of SNPs by simultaneously amplifying up to 558 loci.

7. The Examiner asserts that Brooks et al.. disclose "hot start" PCR.

8. The essence of the Examiner's reasoning is that Mein and Wang both describe multiplex amplification of DNA that includes SNPs, and that modification of the reaction in terms of alteration of the amount of reagents used, as in the presently claimed invention, is "mere optimization", thus obvious, unpatentable modification of the prior art. In this regard, I note that Brooks et al. is cited

only for its teaching of "hot start" PCR methods and adds nothing to the question of obviousness of the principal invention.

6. To demonstrate that the results of successful typing of at least 98% of loci by the instantly claimed method using an amount of DNA at the lower end of the range recited in the present claims, that is at a ratio of 0.1 ng of DNA per SNP site to be typed, 96 loci were simultaneously typed for 20 samples of genomic DNA using the method described in Examples 1 through 3 of the present application, except that 10 ng of DNA were used as the starting material for the amplification reaction, and only SNP loci 1 through 96 described in Example 2 were typed, so that a 96-well plate could be conveniently used.

7. The results of the experiment are shown in the attached Table I. "11" means the sample is homozygous for allele 1. "22" means the sample is homozygous for allele 2. "12" means the sample is heterozygous. "XX" denotes a failure of typing of the locus for that sample. The final column shows the percentage of loci successfully typed in the experiment.

8. The data show that, for all 20 of the samples typed, at least 98% of the loci were successfully typed, and in 14 of 20 samples 100% of the loci were successfully typed.

9. Based on the results of Wang et al., about 85% of the loci would be successfully typed at

the level of simultaneous analysis of 96 loci. See the top of the third column of page 1080 of the reference. Therefore, the finding that more than 98% of 96 loci were successfully typed simultaneously using the method of the present invention must be taken as unexpected.

10. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: June 10, 2008 By _____
Dr. Yusuke Nakamura

Curriculum Vitae

Name: *Yusuke Nakamura*

Position: *Director, Human Genome Center*
Professor, Laboratory of Molecular Medicine
Institute of Medical Science
The University of Tokyo

Director, Center for Genomic Medicine, RIKEN

Education:
1977 *Osaka University Medical School*
1984 *Ph. D. of molecular genetics from Osaka University*

Occupation:
1977–1981 *Second Department of Surgery, Osaka University School of Medicine*
1981–1984 *Research fellow, Institute for Molecular and Cellular Biology, Osaka University*
1984–1988 *Research Associate, Howard Hughes Medical Institute, University of Utah*
1987–1989 *Research Assistant Professor, Department of Human Genetics, University of Utah*
1989–1995 *Head of Biochemistry Department, Cancer Institute, Tokyo*
1994– *Professor, Laboratory of Molecular Medicine, Institute of Medical Science, The University of Tokyo*
1995– *Director, Human Genome Center, Institute of Medical Science, The University of Tokyo*
2005– *Director, Center for Genomic Medicine, RIKEN*

Member in the Editorial (or Advisory) Board for journals
Annals of Human Genetics
Cancer Research (Deputy Editor)
Cancer Science (Editor)
Cell Cycle
Clinical Genetics
Genes Chromosomes & Cancer
International Journal of Oncology
Journal of Human Genetics
Neoplasia

Members in
Japanese Society of Human Genetics (President)
Japanese Cancer Association (board member)

Awards
1992 *Princess Takamatsu Cancer Research Award*
1995 *The Award of the Japanese Society of Human Genetics*
1996 *Takeda Medical Prize*
2000 *Keio Medical Science Prize*
2002 *The Tomizo Yoshida Award of the Japanese Cancer Association*
2004 *The Medal with a Purple Ribbon (for contributions to education and culture)*
2006 *Bulgarian Academy of Medical Science, Foreign Member*
Number of papers published (at May 5, 2007, including in press)

Journal	Number
Am. J. Human Genetics	30
Biochem. Biophy. Research Comm.	16
British Journal of Cancer	8
Cancer	6
Cancer Research	101
Cancer Science	28
Cell	1
Clinical Cancer Research	17
Cytogenetics Cell Genetics	59
Genes Chromosomes and Cancer	39
Genomics	84
Human Genetics	28
Human Molecular Genetics	39
Human Mutation	12
International Journal of Oncology	20
Journal of Human Genetics	96
Jpn. J. Cancer Research	25
Jpn. J. Human Genetics	6
Lancet	5
Molecular Cell	1
Nature	14
Nature Cell Biology	2
Nature Genetics	27
Neoplasia	6
New Eng. J. Med.	4
Oncogene	44
Proc. Natl. Acad. Sci. USA	7
Science	11
Others	183
Total	919

Citations of these papers: 〉50,000 times

http://www.ims.u-tokyo.ac.jp/nakamura/main/pub_list/pub_list.html